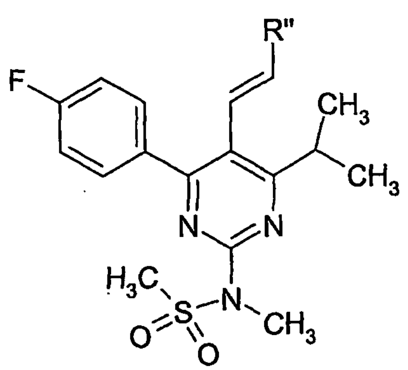
SALTS OF HMG-CoA REDUCTASE INHIBITORS AND USE THEREOF

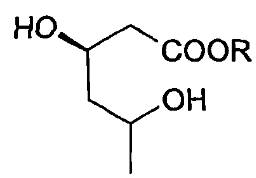
Field of Invention

The present invention relates to salts of HMG CoA reductase inhibitors, and in particular, rosuvastatin amine salts and their use as intermediates in the preparation of rosuvastatin calcium.

Background of the Invention

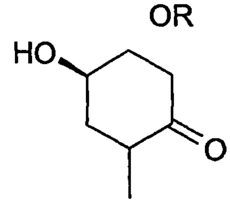
Rosuvastatin is (3R,5S,6E)-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl (methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid, shown as Formula II below, wherein R is a hydrogen atom. Rosuvastatin or its pharmaceutically acceptable salts, such as rosuvastatin calcium of Formula IIa (wherein R is calcium) and rosuvastatin magnesium of Formula IIb (wherein R is magnesium) are antihypercholesterolemic drugs used in the treatment of atherosclerosis.





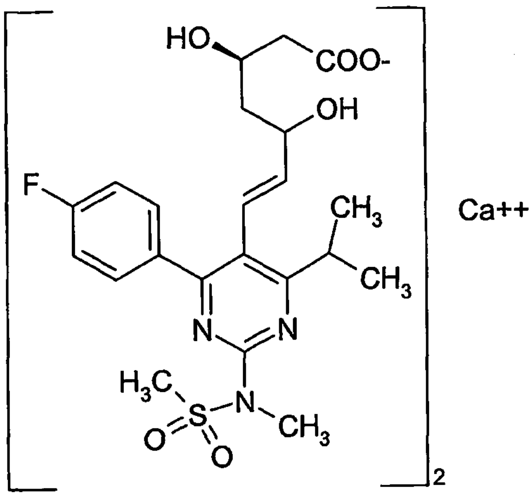
FORMULA A

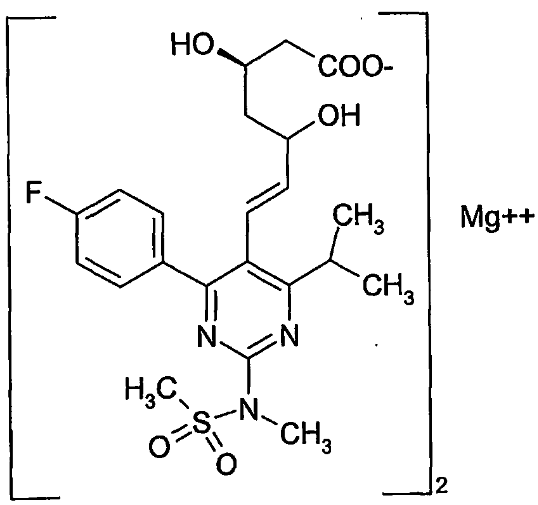
OR



FORMULA B

FORMULA II





FORMULA IIa **FORMULA IIb**

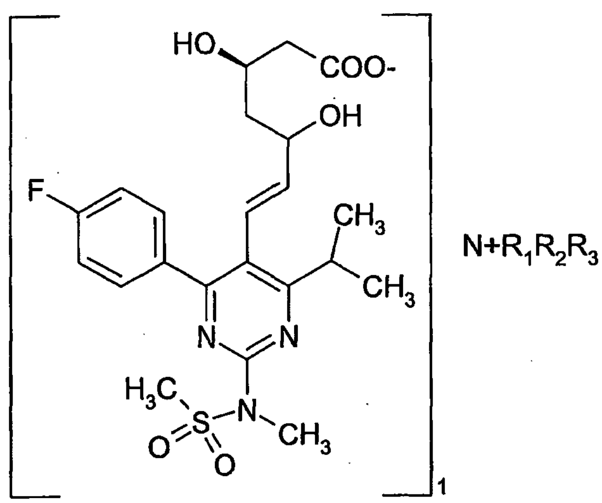
U.S. Patent No. RE 37,314 describes a process for the preparation of amorphous rosuvastatin calcium by dissolving the corresponding sodium salt in water, adding calcium chloride and collecting the resultant precipitate by filtration. U.S. Patent No. 6,589,959 describes a process for the preparation of crystalline Form A of rosuvastatin by warming amorphous rosuvastatin calcium in a mixture of water and acetonitrile, cooling the resultant solution to ambient temperature, and then filtering the product which is then dried at 50°C under vacuum to give crystalline Form A of rosuvastatin calcium. PCT patent application WO 01/60804 describes the preparation of crystalline rosuvastatin salts, namely, ammonium, methylammonium, ethylammonium, diethanolammonium,

tri(hydroxymethyl)-methylammonium, benzylammonium, 4-methoxybenzylammonium, lithium and magnesium salts of crystalline rosuvastatin. A process for preparation of rosuvastatin calcium from all these salts is also described in this patent application.

With the advent of worldwide pharmaceutical regulations, and increased emphasis on drug product quality, it is very important for pharmaceutical companies to produce drug substances having higher purity and lower impurity content.

Summary of the Invention

Amine salts of rosuvastatin of Formula I are provided herein,



FORMULA I

which can be useful as intermediates in the preparation of pharmacologically acceptable salts of rosuvastatin, such as rosuvastatin calcium or rosuvastatin magnesium. Also provided herein are processes for the preparation of amine salts of rosuvastatin. Also provided herein are processes of converting amine salts of rosuvastatin to pharmaceutically acceptable salts of rosuvastatin, such as calcium or magnesium. Also provided herein are pharmaceutical compositions comprising amine salts of rosuvastatin along with pharmaceutically acceptable excipients and/or carriers and methods of treatment of disease in which HMG-CoA reductase is implicated.

While developing commercially viable processes for the production of rosuvastatin or its pharmaceutically acceptable salt, a significant challenge to process chemists is how

to achieve desired high purity and minimize the impurity content. It is now found that particular amine salts of rosuvastatin can be obtained in pure form from rosuvastatin lactone or from rosuvastatin acid, and which can then be used as intermediates in preparation of rosuvastatin or pharmaceutically acceptable salts and the lactone thereof.

The term "amine salts" of rosuvastatin of Formula I refers to an amine salt or solvate, hydrate, crystalline or amorphous form thereof, in which the amine residue has a Formula $NR_1R_2R_3$ wherein independently R_1, R_2 and R_3 are H, straight or branched chain C_{1-15} alkyl or hydroxyalkyl, C_{3-10} single or fused ring optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, alkylcycloalkyl, or independently R_1, R_2 and R_3 can combine with each other to form a C_{3-7} membered cycloalkyl ring or heterocyclic residue containing one or more heteroatoms (selected from S, N or O), with the proviso that the amine is not selected from ammonia, methylamine, ethylamine, diethanolamine, tri(hydroxymethyl)-methylamine, benzylamine, or 4-methoxybenzylamine.

The term "rosuvastatin of Formula II" refers to the free acid of rosuvastatin, wherein R" is of Formula A and R is hydrogen or lactone form of compound of Formula II wherein R" is of Formula B. The term also encompasses salts wherein R in Formula A is selected from metal ions capable of forming a salt or an amino acid residue and esters of rosuvastatin wherein R in Formula A is selected from optionally substituted C_{1-5} alkyl, aryl, cycloalkyl and heterocyclic residues. The term also covers compounds of Formula II which can be present in crystalline, solvate, hydrate or amorphous form thereof.

Detailed Description of the Drawings

Figure 1 is an X-ray diffraction pattern of the cyclohexyl ammonium salt of rosuvastatin, as prepared in Example 1.

Figure 2 is an X-ray diffraction pattern of the diisopropyl ammonium salt of rosuvastatin, as prepared in Example 2.

Figure 3 is an X-ray diffraction pattern of the isopropyl ammonium salt of rosuvastatin, as prepared in Example 3.

Figure 4 is an X-ray diffraction pattern of the dicyclohexyl ammonium salt of rosuvastatin, as prepared in Example 4.

Figure 5 is an X-ray diffraction pattern of the (S) (+)- □-methylbenzyl ammonium salt of rosuvastatin, as prepared in Example 5.

Figure 6 is an X-ray diffraction pattern of amorphous rosuvastatin calcium, as prepared in Example 6, step b).

Figure 7 is an X-ray diffraction pattern of crystalline rosuvastatin calcium, as prepared in Example 6, step c).

Figure 8 is an X-ray diffraction pattern of crystalline rosuvastatin magnesium, as prepared in Example 7.

Detailed Description of the Invention

In one aspect, amine salts of rosuvastatin of Formula I or solvate, hydrate, crystalline or amorphous forms thereof are provided, in which the amine residue has the formula $NR_1R_2R_3$ wherein independently R_1, R_2 and R_3 are H, straight or branched chain C_{1-15} alkyl or hydroxyalkyl, C_{3-10} single or fused ring optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, alkylcycloalkyl, or independently R_1, R_2 and R_3 can combine with each other to form a C_{3-7} membered cycloalkyl ring or heterocyclic residue, containing one or more heteroatoms (S, N or O), with the proviso that the amine is not selected from ammonia, methylamine, ethylamine, diethanolamine, tri(hydroxymethyl)-methylamine, benzylamine, or 4-methoxybenzylamine. In another aspect, amine salts of rosuvastatin of Formula I having purity above 99% and diastereomeric impurity less than 0.5%, are also provided, for example, with purity more than 99.5% and diastereomeric impurity less than 0.25%, or with purity more than 99.75% and diastereomeric impurity less than 0.15%.

In another aspect, a process for preparation of amine salts of rosuvastatin of Formula I is provided. The process comprises:

a) treating rosuvastatin of Formula II with an amine of Formula $NR_1R_2R_3$ wherein independently R_1, R_2 and R_3 are H, straight or branched chain C_{1-15} alkyl or hydroxyalkyl, C_{3-10} single or fused ring optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, alkylcycloalkyl or independently R_1, R_2 and R_3 can combine with each other to form a C_{3-7} membered cycloalkyl ring or heterocyclic residue containing one or more heteroatoms, with

the proviso that the amine is not selected from ammonia, methylamine, ethylamine, diethanolamine, tri(hydroxymethyl)-methylamine, benzylamine, or 4-methoxybenzylamine; and

b) isolating the amine salt of rosuvastatin of Formula I.

Rosuvastatin of Formula II can be dissolved or suspended in an organic solvent and to this mass can be added an amine of Formula $NR_1R_2R_3$ wherein R_1, R_2 and R_3 are as defined above at a temperature of from about –50 to about 100°C. Amine salts of rosuvastatin of Formula I can precipitate from the reaction mass after stirring, which is then isolated, for example, by filtration. The product can optionally be washed with a second organic solvent, in which compounds of Formula I are insoluble or very slightly soluble or sparingly soluble. The product can then suitably be dried to get amine salts of rosuvastatin of Formula I in pure form, which can be further purified by crystallization or any other suitable method such as column chromatography.

The organic solvent used in the reaction is characterized by the fact that rosuvastatin of Formula II is very soluble or soluble in it whereas amine salts of rosuvastatin of Formula I are slightly soluble, very slightly soluble or insoluble in such solvent. Some examples of such organic solvents are: esters such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate and isobutyl acetate; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone; and chlorinated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and ethylene dichloride.

The second organic solvent (in which amine salts of rosuvastatin of Formula I are insoluble (10,000 and over parts of solvent required for 1 part of solute as per United States Pharmacopoeia 2002) or very slightly soluble (form 1,000 to 10,000 parts of solvent required for 1 part of solute as per United States Pharmacopoeia 2002) or sparingly soluble (from 30 to 100 parts of solvent required for 1 part of solute as per United States Pharmacopoeia 2002) can be, for example, cyclopentane, cyclohexane, cycloheptane, hexane, petroleum ether, heptane, diethyl ether, diisopropyl ether or mixtures thereof.

In another aspect, amine salts of rosuvastatin of Formula I or solvate, hydrate, crystalline or amorphous form thereof are provided, in which the amine residue has a

Formula $NR_1R_2R_3$ (wherein independently R_1, R_2 and R_3 are H, straight or branched chain C_{1-15} alkyl or hydroxyalkyl, C_{3-10} single or fused ring optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, alkylcycloalkyl, or independently R_1, R_2 and R_3 can combine with each other to form a C_{3-7} membered cycloalkyl ring or heterocyclic residue containing one or more heteroatoms, with the proviso that the amine is not selected from ammonia, methylamine, ethylamine, diethanolamine, tri(hydroxymethyl)-methylamine, benzylamine, or 4-methoxybenzylamine). These salts can be provided as intermediates for the preparation of rosuvastatin or pharmaceutically acceptable salts, esters and lactones thereof.

Processes provided herein for the preparation of amine salts of rosuvastatin of Formula I are straightforward and simpler, as compared to processes described in, for example, PCT application WO 01/60804, with respect to the number and quantity of solvents used, reaction time and temperature, purity of product obtained and ease of isolating the final product. The amine salts of Formula I as prepared by processes provided herein can be isolated as crystalline solids having a purity of at least above 99.0% and diastereomeric impurity less than 0.5%. These amine salts of Formula I can be easily purified further by simple crystallization technique without significant loss during purification to achieve a purity of above 99.75% and diastereomeric impurity less than 0.5%. Thus, their use as intermediates is substantiated in preparation of rosuvastatin or pharmaceutically acceptable salts, esters and lactone thereof, which are commercially used as drug substances.

In another aspect, processes for the preparation of amorphous or crystalline rosuvastatin calcium of Formula IIa from amine salt of Formula I are provided herein, wherein the process comprises:

a) treating an amine salt of a compound of Formula I with an acid;

b) optionally isolating rosuvastatin acid or a lactone thereof;

c) adding a base and calcium ions;

d) isolating amorphous rosuvastatin calcium; and

e) optionally converting amorphous rosuvastatin calcium to crystalline rosuvastatin calcium.

Rosuvastatin amine salt of Formula I can be treated with an acid, at a pH of about 1 to about 4, to get rosuvastatin lactone, or at pH of about 4.5 to about 5, to get rosuvastatin acid. The reaction can be carried out in the presence of a first organic solvent, optionally containing water, at a temperature of from about -10 to about 100°C. After completion of the reaction, the layers are separated and organic layer after washing with water and/or brine is concentrated completely under vacuum.

The residue obtained when the reaction pH is adjusted between 4.5 to 5 gives rosuvastatin acid as an oily liquid, which can then be dissolved in water and a first organic solvent, and treated with a base and calcium ions to give rosuvastatin calcium, which precipitates from the reaction mass as amorphous solid.

In order to prepare rosuvastatin lactone, the mixture can be stirred at a temperature of about 40 to about 150°C for about 1 to about 50 hours to effect lactonization. After completion of lactonization, the second organic solvent can be removed from the reaction mass, for example, under vacuum, and the residue can be treated with second organic solvent to get the rosuvastatin lactone. The residue can be as such taken in the next step without actually isolating the lactone.

The acid can be, for example, an inorganic mineral acid such as hydrochloric acid, sulfuric acid, nitric acid, or phosphoric acid; or an organic acid such as formic acid, acetic acid and the like.

The first organic solvent can be, for example, lower alkanols, ethers, esters, ketones, polar aprotic solvents, alkyl, aromatic or cycloalkyl hydrocarbons or mixtures thereof. The lower alkanol can be, for example, methanol, ethanol, isopropanol, isobutanol, n-butanol and n-propanol. The ethers can be, for example, tetrahydrofuran, 1,4-dioxane, diethyl ether and diisopropyl ether. The esters can be, for example, ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, butyl acetate and amyl acetate. The ketones can be, for example, acetone, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone. Polar aprotic solvents can be, for example, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide,

acetonitrile and N-methylpyrrolidone. Alkyl, aromatic or cycloalkyl hydrocarbons can be, for example, toluene, benzene, xylene, cyclopentane, cyclohexane, cycloheptane, hexane, petroleum ether, heptane or mixtures thereof.

The second organic solvent (characterized by the fact that rosuvastatin is insoluble or very slightly soluble or sparingly soluble in it) can be, for example, isopropanol, isobutanol, n-butanol, cyclopentane, cyclohexane, cycloheptane, hexane, petroleum ether, heptane, diethyl ether, diisopropyl ether or mixtures thereof.

The lactone can then be dissolved in an organic solvent, optionally containing water, and treated with a base at a temperature of about 10 to about 70°C for about 1 to about 40 hours to effect hydrolysis of the lactone. The reaction mass pH during the reaction can be adjusted to within the range of about 7.5 to about 11 using a base. The solvent can then be removed and the residue can be taken up in water. The aqueous solution can be washed with the first organic solvent as described earlier, and then treated with calcium ions, after which rosuvastatin calcium can precipitate from the aqueous solution as the amorphous solid.

The base can be, for example, sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate.

The calcium ions can be generated by using a calcium compound which can be, for example, calcium chloride, calcium hydroxide, calcium carbonate, calcium acetate, calcium sulphate, calcium borate, calcium tartarate, calcium bromide or any other compound capable of generating calcium ions.

In another aspect, a process for the preparation of amorphous rosuvastatin calcium from amine salt rosuvastatin of Formula I is provided. The process comprises:

a) treating an amine salt of rosuvastatin with a base and a calcium ions; and

b) isolating amorphous rosuvastatin calcium from the reaction mass.

Examples of base and calcium ion generating compounds are described in detail above. The conversion can be easily carried out in presence of water, optionally containing an organic solvent. The reaction temperature can be kept at about -5 to about 100°C.

The organic solvent can be, for example, lower alkanols, ethers, esters, ketones, polar aprotic solvents, alkyl or cycloalkyl hydrocarbons or mixtures thereof. The lower alkanol can be, for example, methanol, ethanol, isopropanol, isobutanol, n-butanol and n-propanol. The ethers can be, for example, tetrahydrofuran, 1,4-dioxane, diethyl ether and diisopropyl ether. The esters can be, for example, ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, butyl acetate and amyl acetate. The ketones can be, for example, acetone, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone. Polar aprotic solvents can be, for example, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone. Alkyl or cycloalkyl hydrocarbons can be, for example, cyclopentane, cyclohexane, cycloheptane, hexane, petroleum ether, heptane or mixtures thereof.

The amorphous rosuvastatin calcium prepared as described above can have a purity of at least 99%, having less than 0.5% of diastereomeric impurity. It can then be crystallized by, for example, methods described in the US Patent No. 6,589,959, to get crystalline rosuvastatin calcium which can be further converted to amorphous rosuvastatin calcium by, for example, methods described in Indian application 1304/DEL/2003.

In another aspect, processes for the preparation of amorphous or crystalline rosuvastatin magnesium of Formula IIb from amine salt of Formula I are provided. The processes comprise:

a) treating an amine salt of a compound of Formula I with an acid;

b) optionally isolating rosuvastatin acid or a lactone thereof;

c) adding a base and magnesium ions;

d) isolating crystalline rosuvastatin magnesium; and

e) optionally converting crystalline rosuvastatin magnesium to amorphous rosuvastatin magnesium.

The process is similar to that described earlier, however magnesium ions are used to prepare rosuvastatin magnesium instead of calcium ions. The product obtained is crystalline rosuvastatin magnesium unlike the amorphous form obtained in case of rosuvastatin calcium.

The magnesium ions can be generated by using a magnesium compound such as, for example, magnesium chloride, magnesium hydroxide, magnesium carbonate, magnesium acetate, magnesium sulphate, magnesium borate, magnesium tartarate, magnesium bromide or any other compound capable of generating magnesium ions.

In another aspect, processes for the preparation of amorphous rosuvastatin magnesium from amine salt of rosuvastatin of Formula I are provided. The processes comprise:

a) treating an amine salt of rosuvastatin with a base and a magnesium ions; and

b) isolating the crystalline rosuvastatin magnesium from the reaction mass.

The process is similar to that described earlier, however, magnesium ions are used to prepare rosuvastatin magnesium instead of calcium ions. The product obtained is crystalline rosuvastatin magnesium unlike the amorphous form obtained in case of rosuvastatin calcium.

The crystalline forms of rosuvastatin magnesium obtained above can be converted to amorphous rosuvastatin magnesium by, for example, processes described in Indian application 1304/DEL/2003.

In another aspect, highly pure rosuvastatin calcium or rosuvastatin magnesium in crystalline or amorphous form thereof is provided, having a purity of at least 99.5% and diastereomeric impurity less than 0.25%.

In another aspect, a cyclohexyl ammonium salt of Formula I (wherein R_1 and R_2 are hydrogen and R_3 is cyclohexyl group) is provided. The cyclohexyl ammonium salt of Formula I has the X-ray diffraction pattern (XRD) as provided in Figure 1.

In another aspect, a diisopropyl ammonium salt of Formula I (wherein R_1 and R_2 are isopropyl groups and R_3 is hydrogen) is provided. The diisopropyl ammonium salt of Formula I has the X-ray diffraction pattern (XRD) as provided in Figure 2.

In another aspect, an isopropyl ammonium salt of Formula I (wherein R_1 and R_2 are hydrogen and R_3 is isopropyl) is provided. The isopropyl ammonium salt of Formula I has the X-ray diffraction pattern (XRD) as provided in Figure 3.

In another aspect, a dicyclohexyl ammonium salt of Formula I (wherein R_1 and R_2 are cyclohexyl groups and R_3 is hydrogen) is provided. The dicyclohexyl ammonium salt of Formula I has the X-ray diffraction pattern (XRD) as provided in Figure 4.

In another aspect, an (S) (+)- □-methylbenzyl ammonium salt of Formula I (wherein R_1 and R_2 are hydrogen and R_3 is (S) (+)- □-methylbenzyl group) is provided. The (S) (+)- □-methylbenzyl ammonium salt of Formula I has the X-ray diffraction pattern (XRD) as provided in Figure 5.

In another aspect, pharmaceutical compositions comprising amine salts of rosuvastatin of Formula I with a pharmaceutically acceptable diluent or carrier are provided.

In another aspect, a method of treating disease conditions wherein HMG-CoA is implicated is provided, which comprises of administering to a mammal in need thereof a therapeutically effective amount of amine salt of rosuvastatin of Formula I.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLES

Example 1: Preparation of Rosuvastatin Cyclohexyl Ammonium Salt

Rosuvastatin acid (2.0 g) was dissolved in ethyl acetate (10 ml) and the solution was cooled to about 0°C. To the solution was added cyclohexylamine and the resultant mass was stirred for 30 minutes at about 0°C. The precipitated solid compound was filtered and washed with hexane and dried under vacuum at 45°C to give title compound (1.6 g) with HPLC purity: 98.78%, and diastereomeric impurity 0.51%.

The compound was further recrystallized from ethyl acetate to obtain pure title compound having purity above 99.5% and diastereomeric impurity less than 0.25%. XRD is as per Figure 1.

Example 2: Preparation of Rosuvastatin Diisopropyl Ammonium Salt

Rosuvastatin acid (2.0 g) was dissolved in ethyl acetate (10 ml) and the solution was cooled to about 0°C. To the solution was added diisopropylamine and the resultant

mass was stirred for 30 minutes at about 0°C. The precipitated solid compound was filtered and washed with hexane and dried under vacuum at 45°C to give title compound (1.8 g) with HPLC purity: 98.6%, and diastereomeric impurity 0.52%.

The compound was further recrystallized from ethyl acetate to obtain pure title compound having purity above 99.5% and diastereomeric impurity less than 0.25%. XRD is as per Figure 2.

Example 3: Preparation of Rosuvastatin Isopropyl Ammonium Salt

Rosuvastatin acid (2.0 g) was dissolved in ethyl acetate (10 ml) and the solution was cooled to about 0°C. To the solution was added isopropylamine and the resultant mass was stirred for 30 minutes at about 0°C. The precipitated solid compound was filtered and washed with hexane and dried under vacuum at 45°C to give title compound (1.6 g), with HPLC purity: 98.4%, and diastereomeric impurity 0.5%.

The compound was further recrystallized from ethyl acetate to obtain pure title compound having purity above 99.5% and diastereomeric impurity less than 0.25%. XRD is as per Figure 3.

Example 4: Preparation of Rosuvastatin Dicyclohexyl Ammonium Salt

Rosuvastatin acid (2.0 g) was dissolved in ethyl acetate (10 ml) and the solution was cooled to about 0°C. To the solution was added dicyclohexylamine and the resultant mass was stirred for 30 minutes at about 0°C. The precipitated solid compound was filtered and washed with hexane and dried under vacuum at 45°C to give title compound (1.9 g), with HPLC purity: 98.8%, and diastereomeric impurity 0.49%.

The compound was further recrystallized from ethyl acetate to obtain pure title compound having purity above 99.5% and diastereomeric impurity less than 0.25%. XRD is as per Figure 4.

Example 5: Preparation of Rosuvastatin (S)-(+)-□-Methylbenzyl Ammonium Salt

Rosuvastatin acid (2.0 g) was dissolved in ethyl acetate (10 ml) and the solution was cooled to about 0°C. To the solution was added (s)-(+)-□-methylbenzyl amine and the resultant mass was stirred for 30 minutes at about 0°C. The precipitated solid

compound was filtered and washed with hexane and dried under vacuum at 45°C to give title compound (1.7 g), with HPLC purity: 98.2%, and diastereomeric impurity 0.54%.

The compound was further recrystallized from ethyl acetate to obtain pure title compound having purity above 99.5% and diastereomeric impurity less than 0.25%. XRD is as per Figure 5.

<u>Example 6: Preparation of Rosuvastatin Calcium from Diisopropyl Ammonium Salt of Rosuvastatin</u>

Step a) Preparation of rosuvastatin lactone from rosuvastatin diisopropyl ammonium salt.

Rosuvastatin diisopropyl ammonium salt (2 gm) was added into mixture of ethyl acetate (10 ml) and water (20 ml) at 25-30°C and the pH of the reaction mass was adjusted to about 3.0 with 6N hydrochloric acid. The layers were separated and the organic layer is washed with water (5 ml). The organic layer was concentrated under vacuum to get an oily crude product, which was mixed with toluene (5 ml). The reaction mass was refluxed for about 6 hours and the solvent was removed under vacuum at 60°C. The residue obtained was stirred with hexane (10 ml) and the separated solid was filtered. Dried the product under vacuum till constant weight at 40-45°C to get rosuvastatin lactone.

Step b) Conversion of rosuvastatin lactone to amorphous rosuvastatin calcium.

Rosuvastatin lactone as obtained in step a) of Example 6 was dissolved in methanol (10 ml) and water (10 ml). To this solution was added, 8% sodium hydroxide solution until the pH of the reaction mass was about 8.5 to 8.7 and stirred for further 3 hours. After ensuring the absence of rosuvastatin lactone by TLC, solvent was removed under vacuum and the aqueous layer was washed with methyl *tert*-butyl ether (8 ml). The traces of methyl *tert*-butyl ether were removed under vacuum and to the aqueous layer added a solution of calcium chloride dihydrate (0.45 gm) in water (2.5 ml) at 20-22°C with vigorous stirring. After complete addition, mixture was stirred for further 2 hours at 20-22°C and filtered, washed the cake with water (2 ml) thrice and then dried at 45°C under vacuum to get amorphous rosuvastatin calcium. The yield was 1.53 gm (83%) (XRD as per Figure 6 showed it to be an amorphous material).

Step c) Conversion of amorphous rosuvastatin calcium to crystalline rosuvastatin calcium

Amorphous rosuvastatin calcium (1.0 gm) was added to a mixture of water (5 ml) and acetonitrile (5 ml) at 15°C. The mixture was warmed to 40°C to obtain complete solution. The mixture was then cooled slowly to 25-30°C and stirred for 16 hours. The crystalline product was separated by filtration at ambient temperature and dried at 50°C under vacuum to give rosuvastatin calcium as white crystals, in a yield of 0.68 gm (68%) (XRD as per Figure 7 showed it to be crystalline material).

Example 7: Preparation of Crystalline Rosuvastatin Magnesium from Rosuvastatin Diisopropyl Ammonium Salt

Rosuvastatin diisopropyl ammonium salt (1.0 g) was added into mixture of ethyl acetate (50 ml) and water (10 ml) and the pH of the reaction mass adjusted to about 3 with hydrochloric acid (6N). The layers were separated and the organic layer is washed with water (3 ml). The organic layer was concentrated under vacuum at 40°C to get oily crude residue which was dissolved in methanol (5 ml) and water (5 ml) and charged a solution of aqueous sodium hydroxide (0.9 ml, 8% w/v) at 25-30°C and stirred for further 30 min. Methanol was removed under vacuum at 40°C. To the resultant aqueous solution was added a solution of magnesium diacetate tetrahydrate (0.25 g, 20% in water) at 35°C under vigorous agitation. The resultant mass was further stirred for 1 hour at RT and solid crystalline product was collected by filtration. The product was dried under vacuum at 50°C, with a yield: 0.8 g (80%) (XRD as per Figure 8 showed it to be crystalline material)